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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SHUKLA, RAM R	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 08/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/021,403	SCHWARTZ ET AL.	
	Examiner	Art Unit	
	Ram R. Shukla	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 November 2003*.

2a)☐ This action is FINAL. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-136* is/are pending in the application.

4a) Of the above claim(s) *14-75 and 89-136* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13 and 76-88* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 December 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/14/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *See Continuation Sheet*.

Continuation of Attachment(s) 6). Other: Notice for Non-compliance with **Nucleotide Sequence Rules.**

DETAILED ACTION

1. Applicant's election without traverse of the invention of group I, claims 1-13 and 76-88 in the reply filed on 11/21/03 is acknowledged.

2. Claims 14-75 and 89-136 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 11/21/03.

3. Claims 1-13 and 76-88 are under consideration.

4. Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Specifically the application fails to comply with CFR 1.821(d), which states:

> (d) Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO: " in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application.

The specification discloses nucleotide and amino acid sequences in figure 1. However, these sequences are not identified by sequence identifiers in the brief description of the figures.

For compliance with sequence rules, it is necessary to include the sequence in the "Sequence Listing" and identify them with SEQ ID NO. In general, any sequence that is disclosed and/or claimed as a sequence, i.e., as a string of

particular bases or amino acids, and that otherwise meets the criteria of 37 CFR 1.821(a), must be set forth in the "Sequence Listing." (see MPEP 2422.03).

For the response to this office action to be complete, Applicants are required to comply with the Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-13 and 76-88 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of improving or enhancing growth or rate of growth in an offspring of a pregnant non-human mammal female, comprising, introducing in the female sow intramuscularly during third trimester of gestation of said offspring a vector comprising a muscle specific promoter operably linked to the nucleotide sequence disclosed in SEQ ID NO 1 or SEQ ID NO 8 wherein said nucleotide sequence is operably linked to a HGH 3' untranslated region, wherein said nucleotide sequence is expressed in the female and wherein the expression of said nucleotide sequence results in improved or enhanced growth or rate of growth of the offspring, does not reasonably provide enablement for other embodiments of the claimed invention. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Instantly claimed invention encompasses inutero fetal gene therapy where any nucleic acid linked to any promoter and any 3' UTR is introduced into any animal any time (before, after or during pregnancy) by any method/route so as to increase the growth of the offspring. However, at the time of the invention, the art

of gene therapy in general and in utero fetal gene therapy were unpredictable and the specification does not provide sufficient guidance as to how an artisan of skill would have been able to practice the claimed invention commensurate with the full scope of the claims without undue experimentation.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The specification as filed teaches injection of a vector pSP-HV-GHRH at 90 days of gestation (in the last trimester of gestation of the offspring) into semitendinosus muscles and after the injection muscle was placed between a set of calipers and electroporated (see examples 7, 14). Applicants' group also reported (Khan et al. Endocrinology 143:3561-3567, 2002, see the methods section and the results; Khan et al. Amer. J. Physiol. 285:E224-E231, 2003, see the abstract and the rest of the article) reported injection of the vector in left tibial anterior muscle. Both the pigs and the rat offspring showed enhanced growth and muscle hypertrophy. While these results demonstrate that GHRH nucleic acid present in the

above vector when given to pregnant non-human females result in the transfer of the GHRH produced in the mother to the fetus and offspring, the state of the art of fetal gene therapy via mother was unpredictable at the time of the invention. Additional, there is no way of controlling the expression of the gene and therefore delivery of the protein to the fetus could not be controlled and as seen this would lead to muscle hypertrophy in the offspring which may not be desirable in a human subject. It is noted that claims 1-4, 6-14 and 76-79, 81-88 recite just a nucleotide sequence, however, there is no evidence in the specification that by introducing any nucleotide sequence in a female the growth of a offspring could be increased or enhanced.

Stribey et al (Fertility and Sterlity 77:645-657, 2002) while reviewing the state of the art of gene therapy during pregnancy, noted (see the abstract):

"Significant problems remain to be overcome including low efficacy of gene transfer, the transient expression of some vectors, safety issue with modified adenoviruses and retroviruses, and ethical concerns".

While office does not consider the issues of ethics and safety, other issues make the art of gene therapy in general unpredictably. The authors further discuss the challenges related to gene therapy on page 645 and 646, table 1. On pages 649-652 and in table 5 the article discusses advantages and disadvantages of various aspects of gene therapy, which indicates that the art of gene therapy was not routine even in 2002. In addition to these general issues of gene therapy, Stribey et al note that placental dysfunction and insufficiency in pregnancy increases the potential of severe health complications in the mother and the fetus, such as preeclampsia and intrauterine growth restrictions (see second full paragraph in the right column on page 653).

In other assessments of the state of gene therapy art, Verma and Somia (Verma IM and Somia N. Nature 389: 239-242. 1997) summarized " In principle, gene therapy is simple: putting corrective genetic material into cells alleviates the symptoms of disease. In practice, considerable obstacles have emerged." They further add " But the problems- such as lack of efficient delivery systems, lack of

sustained expression, and host immune response reactions-remain formidable challenges" (see the abstract). Although more than 200 clinical trials are currently underway worldwide, with hundreds of patients enrolled, there is no single outcome that we can point to as a success story" (see first and second paragraphs in col 1 on page 239).

Anderson (Anderson WF. Nature 392 (SUPP):25-30, 1998) noted that since the approval of first clinical trial of gene therapy protocol in 1990, more than 300 protocols and: "The conclusions from these trials are that gene therapy has the potential for treating a broad array of human diseases and that the procedure appears to carry a very low risk of adverse reactions; the efficiency of gene transfer and expression in human patients is, however, still disappointingly low. Except for anecdotal reports of individual patients being helped, there is still no conclusive evidence that a gene therapy protocol has been successful in the treatment of a human disease."

Finally, Romano et al (Romano et al. Stem Cells 2000; 18:19-39) reporting on the recent developments of gene therapy, noted, " However, the real effectiveness of gene therapy programs is still in question. After a decade of clinical trials, the therapeutic applications of gene transfer technology are still at a rather preliminary stage."

It is noted that these reviews by the leaders in the field of gene therapy are about those gene therapy protocols and applications where the mechanism of action and some efficacy has been determined in animals models and there may be some extrapolatable correlations indicating the therapeutic effects of a particular gene's encoded protein. Even with such results, it is uncertain whether there would be a therapeutic effect when the studies obtained in a mouse model or another animals model is extended to a human subject.

In addition to the issues of unpredictability to humans, the reviews by Anderson, Romano et al and Verma and Somiya discuss the unpredictability with the issues of vectors, promoter, route of administration ect. In summary, the art of gene therapy in vivo was unpredictable at the time of the invention and the

specification as filed does not provide any guidance to address these issues and an artisan of skill would have required undue experimentation to practice the claimed invention commensurate with the full scope of the claims and therefore, limiting the scope of the claimed invention to a method of improving or enhancing growth or rate of growth in an offspring of a pregnant non-human mammal female, comprising, introducing in the female sow intramuscularly during third trimester of gestation of said offspring a vector comprising a muscle specific promoter operably linked to the nucleotide sequence disclosed in SEQ ID NO 1 or SEQ ID NO 8 wherein said nucleotide sequence is operably linked to a HGH 3' untranslated region, wherein said nucleotide sequence is expressed in the female and wherein the expression of said nucleotide sequence results in improved or enhanced growth or rate of growth of the offspring is proper.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 11 and 86 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 11 and 86 dependent on claims 1 and 76 respectively recite that the vector is liposome, a cationic lipid or combination thereof. It is unclear as to how a vector could comprise a liposome of lipid. It is noted that the vector in claim 1 is a nucleic acid that comprises certain embodiments such as promoter, nucleotide sequence etc and could not be a lipid or liposome.

9. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ram R. Shukla whose telephone number is (571) 272-0735 . The examiner can normally be reached on Monday through Friday from 7:30 am to 4:00 p.m. If attempts to reach the examiner by telephone are

unsuccessful, the examiner's supervisor, Amy Nelson, can be reached at (571) 272-0804. The fax phone number for TC 1600 is (703) 872-9306. Any inquiry of a general nature, formal matters or relating to the status of this application or proceeding should be directed to the Dianiece Jacobs whose telephone number is (571) 272-0532.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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